Detection and functional characterization of prion-like protein self-assembly

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The replication of biological information is no longer the exclusive purview of nucleic acids. Information can also be encoded and replicated solely through the self-templated assembly of certain proteins known as prions. We now know that this process occurs frequently, and in ways that are fundamental to human health and disease. On the one hand, a barrage of recent discoveries implicates prion-like mechanisms for the cell-to-cell progression of protein misfolding in ALS, Alzheimer's, Parkinson's, and Huntington's diseases. On the other hand, prion-like switches have been proposed to functionally encode molecular memories and to transduce cellular signals. We seek to explore the breadth of biological effects mediated by prion-like self assembly and to decipher the rules that govern it. We do so by investigating prion-like proteins from two extremes of conformation space: intrinsically disordered regions commonly involved in gene regulation, and globular death domains involved with mammalian innate immunity and programmed cell death. Our findings with these proteins establish a general role for prion formation in cell fate determination. First, we have discovered that prions formed by certain low complexity transcription factors in budding yeast act as environmentally-responsive epigenetic determinants of multicellularity[1]. We have further found that the different growth forms produced by prion switching exhibit frequency-dependent fitness interactions that drive primitive metabolic divisions of labor. Second, we have discovered that the mammalian death domain superfamily proteins, MAVS and ASC, form bona fide prions that functionally commit cells to antiviral and inflammatory responses, respectively[2]. We further demonstrated that the principles of prion-driven immune signaling are conserved all the way into fungi. Finally, we have developed a powerful new method that enables high throughput detection and quantification of prion-like self assembly. This method has already revealed new prions and prion modulators, and will dramatically accelerate future such discoveries.

1. Holmes DL, Lancaster AK, Lindquist S, Halfmann R. Heritable remodeling of yeast multicellularity by an environmentally responsive prion. Cell 2013; 153:153-65.
2. Cai X, Chen J, Xu H, Liu S, Jiang QX, Halfmann R, Chen ZJ. Prion-like polymerization underlies signal transduction in antiviral immune defense and inflammasome activation. Cell 2014; 156:1207-22.